II. REMARKS

Claims 1 to 41 are pending in the subject application.

Claims 25 to 41 have been withdrawn from consideration as a result of a requirement for restriction. Claims 1 to 24 were examined and stand variously rejected.

Claims 2, 5-7, 17-17 and 21-24 have been amended to more specifically point out and distinctly claim the subject matter that Applicants regard as the invention. For example, claim 2 has been amended to a method for preparing substantially homogenous IKK protein complex comprising at least an IKK γ subunit. Support for amended claim 2 is found in the specification on page 11, lines 15 to 17; page 12, lines 10 to 12; pages 13 through 17 and on page 21, line 1.

Claims 3, 4, and 8-16 have been canceled without prejudice or disclaimer. Applicants expressly reserve the right to file one or more claims to the same or similar subject matter.

In view of the preceding amendments and the remarks that follow, reconsideration and withdrawal of the rejections of the claims is respectfully requested.

Examiner Interview Summary

Applicants and their representative thank the Examiner for the courtesy and assistance extended to them during the November 23, 2005 telephonic interview. The interview was helpful to clarify the remaining issues and hopefully, move the claims onto allowance.

Objections to the Claims

Claims 1 and 15 were objected to for alleged informalities that will be removed upon entry of the above amendments to the claims. Without conceding the correctness of the Office's position and in a sincere effort to place the claims in condition for allowance, claims 1 and 5 have been canceled without prejudice to Applicants' right to

file the same or similar claims in a related application. In view of the cancellation of these claims, reconsideration and withdrawal of the objections are respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims 4-9 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office alleged that claim 4 is confusing in the recitation "said selection marker is leucine, histidine, tryptophan, or uracil" as leucine, histidine, tryptophan, and uracil can not be comprised within a vector.

Claim 4 has been canceled without prejudice or disclaimer.

The Office also noted that claims 5 and 6 are confusing in the recitation of "said expression vectors contain a tag" and "said tag is myc, HA, or FLAG 6his" as vectors cannot comprise peptide tags. The Office further noted that the "or" in claim 6 should be correctly placed following the word "FLAG".

Claims 5 and 6 have been amended in a sincere effort to remove the grounds for rejection.

The Office stated that claim 7 (upon which claims 8 and 9 depend) is confusing in the recitation of "said yeast expression vectors contain an inducible promoter or a constitutive promoter" as the vectors are limited in claim 1 (from which Claims 7-9 depend) to comprising inducible promoters. Claim 14 allegedly antecedent basis for "said IKKa" in claim 11 and "said IKKB" in claim 10. Claim 15 allegedly lacks antecedent basis for "said leu(met) vector". Claim 16 allegedly is confusing in the recitation "wherein constitutive expression is induced under the alcohol dehydrogenase promoter" as the vectors are limited in claim 1 (from which Claim 16 depends) to comprising inducible promoters.

Claim 22 and 23 were objected to for allegedly lacking antecedent basis for "said purified IKK protein".

Claim 22 was objected to for use of the term "substantially homologous to IKK isolated from wild-type cells" on the ground that the term "substantially homologous" is a relative term which renders the claim indefinite. Furthermore, the Office argued that claim does not define what cells are the "wild-type" cells such that a skilled artisan would even know what the reference protein is.

Claims 7, 22 and 23 have been amended to remove the grounds for rejection.

In sum, without conceding the correctness of the Office's position, the rejected claims have been amended or canceled in a sincere effort to overcome the grounds for rejection. In view of these amendments, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 112, second paragraph is respectfully requested.

35 U.S.C. § 103

Claims 1-13, 15, 17-20 and 22-24 (renumbered) stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over either Li et al. or Rothwarf et al. in view of Epinat et al.

The Office maintained the rejection of the claims over the combination of the cited references and noted that Applicants' prior remarks were directed to studying IKK complexes in mammalian cells while the claims are directed to reconstituting IKK complexes. Li et al. and Rothwarf et al. were cited for teaching the expression of active IKK complexes in mammalian cells.

The Office previously opined that Epinat et al. is relevant to the claimed invention because it was well known at the time the invention was made that the IKK complex is part of the NF-kB signaling pathway. The Office argued that accordingly, it would have been obvious to one of ordinary skill in the art to reconstitute the IKK complex in a yeast

host cells by expressing the IKK subunit genes of Li et al. or Rothwarf et al. in yeast using any known yeast expression vector or yeast expression vectors as taught by Epinat et al.

Applicants respectfully traverse. Applicants agree that the cited prior art (namely Li et al. or Rothwarf et al.) teaches the reconstitution of IKK complexes in mammalian systems while the claimed invention is to the reconstitution of IKK complexes in yeast. However, the combination of references fails to render obvious the amended claims because the combination fails to teach or suggest a method for reconstituting substantially homogenous IKK protein complex comprising at least the IKK γ subunit. Applicants were the first to prepare and isolate substantially homogenous IKK protein complex comprising the IKK γ subunit. Mammalian systems do not form substantially homogenous complex because the exogenous IKK gene products would complex with the endogenously produced IKK gene products. After failure in the mammalian system, insect cell were the system of choice, but they also did not produce substantially homogenous IKK complex.

As Applicants point out in their specification on page 4, line 17 through page 5, lines 16:

> "In order to effectively study the structure, function and regulation of IKK, efficient means for producing and isolating IKK must be employed. Bacteria, Sf 9 cells, and mammalian cell culture have been described for the production and isolation of IKK, but each has substantial drawbacks. For example, IKK expressed in bacteria forms large aggregates which are not native or functional.
>
> IKK.alpha. and IKK.beta. have been expressed alone and in combination in Sf 9 cells (12, 42). However, in the baculovirus system, co-expression of two or all three subunits of IKK is technically difficult. In addition, insect cells contain IKK-related proteins and signaling pathways that can activate IKK (42).
>
> Sf 9 and mammalian systems also have the disadvantages of endogenous IKK and redundant factors that are not found with yeast. Studying signal transduction directly in mammalian or other higher eukaryotic cells is difficult because many signaling pathways have similar

and redundant factors, and many of the signal transduction pathways intersect and act upon each other. Because IKK is a large complex composed of three different subunits, there may be multiple complexes of IKK which exist to respond to different signals. Furthermore, IKK responds to over 150 signals, studying IKK in mammalian cells is particularly difficult.

A popular method in signal transduction research is to use mammalian cell culture, such as HeLa cells or mouse embryonic fibroblasts, to overexpress a wild type or dominant negative protein in and to test for any effect on IKK activity. Cell culture can be used to show if a protein at least has the potential to be involved in a given network, but it has inherent problems. First, it is difficult to determine if the overexpressed protein acts directly or indirectly. Second, when an enzyme or regulatory protein is expressed at higher than normal levels, it may associate with proteins and networks where it may not normally localize. As a result, the protein may act non-specifically and yield misleading results.

Mechanistic analysis is also complicated in both Sf 9 and mammalian cells due to endogenous proteins. For example, there may be multiple existing IKK complexes in a given cell. Expressed mutated forms of IKK are directed into heterocomplexes containing endogenous proteins, and the effect of the mutation may be lost in a background of these endogenous proteins (44). In some situations, one might try to overcome this by expressing the mutated form at very high levels, but this often results in obscured results due to non-specificity. For example, proteins expressed in cells can interact with non-physiological partners due to the weak similarities in the interaction domains that exist among many proteins of similar functions and results in non-specific activating or inhibiting effects."

Reconsideration and withdrawal of the rejection of the claims is respectfully requested.

Claims 14, 15, and 21 also stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Li et al or Rothwarf et al. in view of Epinat et al., as applied to claims 1-13, 126-20, and 22-23 above, and further in view of either or both of Mumberg et al. or page 23 of the 1999 Stratagene catalog.

Claims 14 and 15 have been canceled without prejudice or disclaimer. Claim 21 has been amended and Applicants respectfully traverse the rejection of claim 21 for the

reasons provided above. The addition of Mumberg et al. or the Stratagene catalog fails to overcome the limitations of the cited art. Reconsideration and withdrawal of the rejection is respectfully requested.

III. CONCLUSION

If a telephone interview would advance prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below. In the unlikely event that the transmittal letter is separated from this document and/or the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-0872** referencing 064189-0501. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date: December 28, 2005

By _____

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